

**APPENDIX C.**

**SUMMARY OF SAFETY AND EFFECTIVENESS (*REVISED*)**

## **SUMMARY OF SAFETY AND EFFECTIVENESS (*REVISED*)**

The originally submitted Summary of Safety and Effectiveness for INTERGEL® Adhesion Prevention Solution is attached, with the following changes.

### **Additions to the text:**

1. Revised statement of intended use (Page 1)
2. Summary results of a supplemental animal safety study (Page 12)
3. Clarification of text regarding adhesion scoring methodology (Page 21)

### **Highlights to the original text (sections relevant to the proposed revised statement of intended use):**

1. Clinical trial results comparing INTERGEL® Solution and lactated Ringer's solution on AFS scores (page 23).
2. Incidence of reformed adhesions and adhesion formation at surgical sites (page 22).

### III. SUMMARY OF SAFETY AND EFFECTIVENESS

#### A. GENERAL INFORMATION

Device Generic Name: Absorbable Adhesion Barrier  
Device Trade Name: INTERGEL™ Adhesion Prevention Solution  
Applicant's Name and Address: Lifecore Biomedical, Inc.  
3515 Lyman Boulevard  
Chaska, MN 55318-3051

Right of Reference to Other Files: N/A

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Manufacturing Site Name and Address: Lifecore Biomedical, Inc.  
3515 Lyman Boulevard  
Chaska, MN 55318-3051

Modular PMA Number: M980022  
PMA Application Number: PMA990015  
Date of Panel Recommendation: TBD  
Date of Notice of Approval to the Applicant: TBD

#### B. INDICATIONS FOR USE

##### Revised:

*INTERGEL® Solution is a single-use, intraperitoneal instillate indicated to reduce the likelihood of developing moderate or severe postoperative adnexal adhesions in patients undergoing adhesiolysis or myomectomy during conservative gynecological pelvic surgery by laparotomy, when used as an adjunct to good surgical technique. INTERGEL® Solution was also shown to reduce adhesion reformation to sites in*

*addition to the adnexa, and adhesion formation at surgical sites, including the anterior abdominal incision.*

**Originally Proposed:**

INTERGEL Solution is indicated for use as a single use, intraperitoneal instillate for reduction of adhesions following gynecological pelvic surgery. It has been shown to reduce the incidence, extent and severity of post-surgical adhesions throughout the abdominal cavity when used as an adjunct to good surgical technique during laparotomy procedures during laparotomy procedures.

**C. DEVICE DESCRIPTION**

INTERGEL™ Adhesion Prevention Solution is a sterile, nonpyrogenic, amber colored, viscous solution of sodium hyaluronate, which has been ionically crosslinked with ferric ions and adjusted to isotonicity with sodium chloride via a proprietary process which avoids precipitation of insoluble ferric hyaluronate and results in a gel formation.

INTERGEL™ Solution is indicated for use as an intraperitoneal instillate for reduction of adhesions following peritoneal cavity surgery. It has been shown to reduce the incidence, extent and severity of adhesions throughout the abdominal cavity when used as an adjunct to good surgical technique through the physical effect of providing a transient viscous, lubricious coating on the peritoneal surfaces, minimizing tissue apposition during the critical period of fibrin formation and mesothelial regeneration following surgical procedures. Lymphatic drainage is the primary elimination pathway for intraperitoneal administered INTERGEL Adhesion Prevention Solution. The elimination half-life ( $T_{1/2}$ ) of INTERGEL Solution has been estimated to be approximately 51 hours. Thus, the majority of the 300 mL INTERGEL Solution instillation would be expected to clear the peritoneal cavity in 5 to 7 days.

INTERGEL™ Solution is packaged in a 300 mL low density polyethylene bellows-type bottle, which is provided sterile in a plastic tray using a Tyvek® lid. When stored at refrigeration (2-8 °C) and controlled room temperature (15 - 30°C), INTERGEL™ has a stable shelf life of 18 months. Ongoing stability studies are anticipated to support at least 24-month shelf life, as is the case with INTERGEL™ in vials.

**D. PRECAUTIONS, WARNINGS AND CONTRAINDICATIONS FOR USE:****1. CONTRAINDICATIONS FOR USE**

The use of INTERGEL Adhesion Prevention Solution is contraindicated in the presence of frank infection.

**2. WARNINGS**

INTERGEL Solution has not been studied in patients with a history of hemochromatosis, or in patients who are unable to process large fluid loads, such as patients with congestive heart failure.

The safety and effectiveness of INTERGEL Solution has not been evaluated in clinical studies in the presence of malignancies in the abdominopelvic cavity.

The safety and effectiveness of INTERGEL Solution has not been evaluated in patients less than 18 years of age.

Clinical studies have not been conducted in pregnant women or women who have become pregnant within the first month after exposure to INTERGEL Solution. Therefore, this product is not recommended for use during pregnancy. Following the use of INTERGEL Solution, it is advised to avoid conception during the first complete menstrual cycle.

INTERGEL Solution has not been studied in patients with significant hepatic or renal disorders nor in patients having surgery which involves opening of the gastrointestinal or urinary tract.

**3. PRECAUTIONS**

The safety and effectiveness of INTERGEL Solution in combination with other adhesion prevention products, peritoneal instillates, and/or medications administered within the abdominopelvic cavity have not been established in clinical studies.

In clinical studies of INTERGEL Solution, 300 mL of solution per patient were instilled into the peritoneal cavity. The safety and effectiveness of larger or smaller volumes have not been established. Foreign body reactions may occur with INTERGEL Solution, as with any implanted material.

Store at 2-30° C (36-86° F), refrigerated or controlled room temperature.

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Prior to peritoneal instillation, INTERGEL Solution should be warmed to body temperature. However, do not allow the product to remain at this temperature in excess of 24 hours.

#### **E. ALTERNATIVE PRACTICES AND PROCEDURES:**

Alternative practices used to reduce adhesion formation are numerous, including minimization of tissue handling, avoidance of foreign particles (e.g., talc, lint) and meticulous hemostasis. In addition, numerous adjuvants, including antibiotics, corticosteroids, anticoagulants and crystalloid solutions to name a few, are used although safety and effectiveness has never been demonstrated. Of these, instillation of 300-500 mL of a crystalloid solution, such as lactated Ringer's solution appears to be the most common.

Alternative products approved for the purpose of reducing adhesion formation include; INTERCEED® (TC7) Absorbable Adhesion Barrier (Johnson and Johnson Medical, Inc.), SEPRAFILM™ Bioresorbable Membrane (Genzyme Corp.) and Preclude Surgical Membrane (W.L. Gore & Associates). Among the above, INTERCEED® and SEPRAFILM™ have shown the most demonstrable effectiveness and do not require a subsequent surgery for their removal, but as is inherent with barrier fabric or film products, the effects are localized and therefore site specific.

#### **F. MARKETING HISTORY:**

INTERGEL Adhesion Prevention Solution has been distributed to those markets where regulatory approval has already been obtained or was not required. As of September 30, 1998, approximately 600 units of INTERGEL Solution had been distributed in Europe.

INTERGEL Adhesion Prevention Solution has not been withdrawn from the market for any reason related to the safety or effectiveness of the product.

#### **G. ADVERSE EFFECTS:**

The type and frequency of adverse events reported are consistent with events typically seen following surgery.

The following adverse events were observed during a randomized, double-masked, multi-center study comparing the safe and effective performance of INTERGEL Solution (300 mL), in reducing adhesions following laparotomy surgery in relation to lactated Ringer's solution (300 mL) among 281 patients (INTERGEL Solution: 143 patients; lactated Ringer's solution: 138 patients).

### Incidence of Commonly ( 5%) Reported Adverse Events: Number (%) of Patients

Body System Preferred Term	LUBRICOAT® Gel (N=143)	lactated Ringer's Solution (N=138)
<b>Body as a Whole</b>	<b>143 (100)</b>	<b>137 (99.3)</b>
Pain	122 (85.3)	111 (80.4)
Headache	45 (31.5)	37 (26.8)
Abdominal pain	39 (27.3)	42 (30.4)
Fever	25 (17.5)	19 (13.8)
Back pain	13 (9.1)	7 (5.1)
Incision, inflammation	8 (5.6)	8 (5.8)
Incision pain	9 (6.3)	13 (9.4)
Allergic reaction	3 (2.1)*	10 (7.2)
<b>Digestive</b>	<b>106 (74.1)</b>	<b>100 (72.5)</b>
Nausea	66 (42.6)	65 (47.1)
Constipation	47 (32.9)	56 (40.6)
Flatulence	35 (24.5)	35 (25.4)
Vomiting	13 (9.1)	14 (10.1)
Dyspepsia	14 (9.8)	10 (7.2)
<b>Urogenital</b>	<b>44 (30.8)</b>	<b>40 (29.0)</b>
Dysmenorrhea	25 (17.5)	22 (15.9)
<b>Nervous</b>	<b>37 (25.9)</b>	<b>40 (29.0)</b>
Insomnia	20 (14.0)	22 (15.9)
Dizziness	15 (10.5)	13 (9.4)
<b>Respiratory</b>	<b>30 (21.0)</b>	<b>26 (18.8)</b>
Cough, increased	11 (7.7)	8 (5.8)
Rhinitis	8 (5.6)	7 (5.1)
<b>Cardiovascular</b>	<b>15 (10.5)</b>	<b>15 (10.9)</b>
Tachycardia	4 (2.8)	7 (5.1)
<b>Hemic and Lymphatic</b>	<b>19 (13.3)</b>	<b>16 (11.6)</b>
Anemia	12 (8.4)	13 (9.4)
<b>Skin</b>	<b>13 (9.1)</b>	<b>13 (9.4)</b>
Pruritus	8 (5.6)	10 (7.2)

\* Statistically significantly different from lactated Ringer's solution, p=0.048, Fisher's Exact test.

## H. SUMMARY OF TOXICITY AND BIOCOMPATIBILITY STUDIES:

Preclinical toxicity and biocompatibility studies conducted in support of the safety of INTERGEL™ Adhesion Prevention Solution included 1) *in vitro* acute cytotoxicity, 2) *in vivo* acute cytotoxicity, 3) multiple-dose sub-chronic toxicity, 4) dermal sensitization, 5) pyrogenicity, 6) hemolysis, and 7) reproductive toxicity.

The studies were performed in accordance with the Good Laboratory Practice Regulations as presented by the Food and Drug Administration (FDA) and published in the Federal Register, 1 April 1988, 21 CFR Part 58, Subparts A through J (excluding H and I). The studies were conducted by the Department of Pathology, Toxicology, and Surgery at Ethicon, Inc. in Somerville, New Jersey 08876 or at various contract laboratories from late

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1992 through early 1994. The studies were selected based on the recommendations of the "Tripartite Biocompatibility Guidance for Medical Devices" for an internally implanted device with "short-term" contact (defined as 5 minutes to 29 days) with tissue and tissue fluids and also reflect the testing recommendations of the International Organization for Standardization (ISO) Guidelines 10993-1 (Biological Evaluation of Medical Devices Part 1: Guidance on Selection of Tests), and FDA's Modified Matrix for Biocompatibility Testing for tissue/bone implant devices with prolonged contact (24 hours to 30 days).

Toxicity and biocompatibility evaluations were conducted *in vitro* in L929 mouse fibroblast cells and *in vivo* in mice, rats, rabbits, guinea pigs, and/or dogs with durations of treatment ranging from single dose to repeat doses over a 28-day period.

The toxicity and biocompatibility studies conducted with INTERGEL demonstrated that this device is non-cytotoxic to L929 mouse fibroblast cells *in vitro*, non-toxic in mice, rats, rabbits, and dogs *in vivo* acutely and sub-chronically, non-hemolytic to erythrocytes in rabbit blood, non-pyrogenic in rabbits, non-sensitizing in guinea pigs following intradermal and topical induction and subsequent topical challenge, and non-toxic to fertility and reproductive parameters when the dosing interval was considered.

#### **1. In Vitro Acute Cytotoxicity:**

The cytotoxicity of INTERGEL was evaluated in cultures of L929 mouse fibroblast cells following standard procedures for the agar overlay assay. In this study, the positive control cultures showed severe cytotoxic effects, whereas the INTERGEL test cultures and the negative control cultures showed no cytotoxic effects. The results of this study demonstrated that INTERGEL is non-cytotoxic.

#### **2. In Vivo Acute Toxicity:**

Seven acute toxicity studies were conducted with INTERGEL administered intraperitoneally (i.p.) using Swiss-Webster mice, Fischer rats, New Zealand White rabbits, and Beagle dogs.

In the acute toxicity studies, INTERGEL did not produce significant treatment-related clinical signs of toxicity, effects on body weight or weight



gain, or gross lesions following intraperitoneal administration at dose volumes up to 20 mL/kg in sexually immature Fischer 344 rats, 50 mL/kg in Beagle dogs, 100 mL/kg in Swiss-Webster mice and sexually mature Fischer 344 rats, and 150 mL/kg in New Zealand White rabbits.

One Beagle dog exhibited transient, systemic toxicity following i.p. administration of 100 mL/kg INTERGEL and clinical signs of toxicity and mortality were observed at a dose volume of 150 mL/kg in Swiss-Webster mice and sexually immature Fischer 344 rats. Transient reduction in food consumption and fecal output, effects on body weights and weight gains, changes in various clinical pathology parameters (only at the high dose), and granulomatous peritonitis were also observed in sexually immature Fischer 344 rats following i.p. administration at dose volumes from 30 to 100 mL/kg INTERGEL. The adverse systemic toxicity in the sexually immature Fischer 344 rats appears to be idiosyncratic, especially since older rats of the same strain and in one study, the same batch, did not experience the same toxicity or constellation of gross lesions associated with the peritonitis.

Although, the no effect level in the young, sexually immature rats (i.e., 25 mL/kg) is only five times the anticipated clinical instillation volume of INTERGEL (i.e., 5 mL/kg), there is an adequate safety margin between the clinical dosage and the maximum dose volumes which did not produce adverse effects in dogs (10-fold), mice and sexually mature rats (20-fold), and rabbits (30-fold) to conclude that INTERGEL is safe for use in humans.

### **3. Multiple-Dose Sub-Chronic Toxicity:**

The toxicity of INTERGEL following repeated dose administration was evaluated using Beagle dogs. In the multiple dose toxicity studies, no mortality occurred in animals injected i.p. with INTERGEL at dose volumes up to 15 mL/kg/dose every third day for 28 days. There were no treatment-related differences in clinical pathology (i.e. hematology, coagulation, blood chemistry and urinalysis) or in organ weights. The only treatment-related changes apparent upon gross or microscopic examination consisted of an accumulation of an iron-containing residue of the formulation in the lymph nodes draining the abdominal cavity, in mesothelial cells covering the abdominal viscera and/or in macrophages in the omentum or on the serosal surface of the abdominal and pelvic viscera.

In summary, no evidence of systemic toxicity was observed in dogs from repeated intraperitoneal injection of INTERGEL at dosage levels of 5, 10 and 15 mL/kg/dose. All gross and microscopic tissue changes were attributed to the invasive administration procedure or to cellular accumulation of an iron-containing residue of INTERGEL.

#### **4. Dermal Sensitization:**

The dermal sensitization potential of INTERGEL was evaluated using Hartley-derived albino guinea pigs. The topical challenge results of this study demonstrated that INTERGEL is not a contact sensitizer in guinea pigs following intradermal and topical induction and subsequent topical challenge.

#### **5. Pyrogenicity:**

The ability of INTERGEL to induce a febrile response following intravenous injection was evaluated using New Zealand White rabbits. The maximum temperature rise for the rabbits injected with diluted INTERGEL was below the 0.5°C USP requirement. The results of this study demonstrate that INTERGEL is non-pyrogenic.

#### **6. Hemolysis:**

The potential hemolytic effects of INTERGEL was evaluated using New Zealand White rabbit red blood cells. The absorbance values were found to correspond to a hemolysis value of 0.6%. Since a mean hemolysis value of 5% or less is considered non-hemolytic, the results of this study demonstrate that INTERGEL is not hemolytic to rabbit red blood cells.

#### **7. Reproductive Toxicity:**

The potential toxic effects of INTERGEL on reproductive capabilities were evaluated using female Sprague-Dawley rats. The studies were designed to evaluate F0 estrous cycles, mating, conception, parturition, lactation and weaning, as well as F1 survival, growth and development.

In the fertility and general reproductive toxicity study of INTERGEL in rats, dose volumes of 5, 15, and 25 mL/kg given i.p. every third day beginning 19 days prior to cohabitation until gestation day 6 produced no treatment-related effects on fertility or reproductive parameters, except for slight to significant reductions in the mean number of implantation sites and viable

fetuses depending upon the volume of INTERGEL administered. In a subsequent study, this effect, presumably due to the viscous physical presence of the INTERGEL in the peritoneal cavity, was significantly reduced when dosing with INTERGEL (25 mL/kg/dose) was stopped one day prior to cohabitation and eliminated when dosing was stopped seven days prior to cohabitation. Again, no other treatment-related effects on fertility or reproductive parameters were observed in these studies.

## **8. Conclusions of Toxicity and Biocompatibility Testing:**

The toxicity and biocompatibility studies conducted with INTERGEL demonstrated that this device is non-cytotoxic to L929 mouse fibroblast cells *in vitro*, non-toxic in mice, rats, rabbits, and dogs *in vivo* acutely and sub-chronically, non-hemolytic to erythrocytes in rabbit blood, non-pyrogenic in rabbits, non-sensitizing in guinea pigs following intradermal and topical induction and subsequent topical challenge, and non-toxic to fertility and reproductive parameters when the dosing interval was considered.

## **I. SUMMARY OF PRECLINICAL STUDIES:**

### **1. Formulation, Effectiveness, and Ancillary Studies**

#### **a. Preclinical Efficacy Studies**

Numerous studies were performed to determine the formulation of INTERGEL™ Solution, using primarily two animal models to investigate the effects of peritoneal instillation of FeHA gels on adhesion formation; the rabbit uterine horn simple abrasion model and the rabbit cecal/large bowel/sidewall abrasion model.

When instilled prior to closing the abdomen, FeHA was found to significantly reduce adhesion formation in both a rabbit cecal/large bowel/side wall model and a rabbit uterine horn abrasion model when compared to surgical controls ( $p < 0.05$ ). Of the various formulations of FeHA gels tested, INTERGEL™ Adhesion Prevention Solution (INTERGEL™ Solution), a low viscosity, 90% crosslinked FeHA gel neutralized with a mixture of ammonia and sodium hydroxide and made isotonic with saline, was maximally effective in the rabbit models tested.

## **b. Preclinical Effectiveness Studies**

### **i) Effectiveness of INTERGEL™ Solution**

Once the critical formulation variables were identified and their effects on the efficacy of FeHA evaluated, a final formulation of INTERGEL™ Adhesion Prevention Solution was selected for clinical evaluation. INTERGEL™ Solution was tested against a low viscosity HA formulation in the rabbit cecal/large bowel/sidewall abrasion model.

Animals received 15 mL of INTERGEL™ Solution or HA; those in the surgical group did not receive any treatment. Adhesions were evaluated seven ( $\pm 1$ ) days later. Adhesions to the sidewall were prevented in all animals treated with INTERGEL™ Solution (N=6); whereas in animals treated with HA, 40% of the sidewall was involved in adhesions compared with 66% in control animals. The number of sidewalls with no adhesions was also evaluated. INTERGEL™ Solution completely prevented adhesions to all sidewalls (6 of 6 animals), whereas HA completely prevented adhesions to the sidewall in only 2 of 7 animals, compared to 0 of 7 control animals.

### **ii) Preclinical Ancillary Studies with INTERGEL™ Solution**

#### **• Effects on Wound Healing**

The effects of INTERGEL™ Solution on colonic anastomosis and incision line wound healing were evaluated in female Long-Evans rats. A ventral midline incision was made to expose the abdominal cavity and the cecum and ascending colon were exteriorized. The ascending colon was transected at a point approximately 2.5 cm aboral to the ileocecal junction and the transected ends were anastomosed with plain gut suture. The cecum and ascending colon were returned to the abdomen. One of the following test solutions was applied to the colonic anastomosis and adjacent peritoneum: 15 mL/kg saline control, 5 mL/kg INTERGEL™ Solution, or 15 mL/kg INTERGEL™ Solution. A fourth group of animals served as the sham controls and did not receive any treatment except for surgery. The abdominal wall, skin and subcutaneous tissues were closed with suture.

Seven and 21 days following surgery, animals were sacrificed after being fasted for the previous 24 hours. Adhesions surrounding the colonic anastomotic site were left intact but trimmed of excess tissue. An approximate 5 to 7 cm length of colon (including the anastomotic site) was dissected away from the abdominal cavity to perform the burst/leak test. Burst strength measurements were performed on a ligated/clamped segment of colon containing the anastomosis by controlled infusion of air into the lumen, until bursting or leakage of the colon occurred. Intraluminal pressure was continuously recorded during the burst strength determination.

A section of the ventral abdominal wall including the incision line was excised from each animal and the suture removed. Tissue thickness and width measurements were recorded and the tissues were tested in tension until failure using an Instron Universal Testing Instrument with crosshead speed set at 5 in/min. Breaking strength values were recorded.

The results of this study demonstrated that intraperitoneal administration of INTERGEL™ Solution at dose volumes up to 15 mL/kg following surgery does not adversely affect healing of colonic anastomoses or incisional wounds in rats.

- Effects on Infection Potentiation

The ability of INTERGEL™ Solution to potentiate infections caused by implantation of fecal material into the abdomen was evaluated in female Sprague-Dawley rats. Animals were divided among the surgical control group, Ringer's Lactate, Hyskon, or INTERGEL™ Solution. Peritonitis was induced in the animals by implanting a double walled gelatin capsule containing a mixture of cecal/fecal contents from hamburger-fed rats, peptone yeast broth, glucose and barium sulfate in the peritoneum on the right side through a midline incision. Prior to closure of the wound, the assigned test material was applied to the area surrounding the capsule. Animals in the surgical control group received the capsule only. The animals were observed daily for 11 days for signs of morbidity and mortality. Those that died during the observation period were necropsied to confirm the presence of acute bacterial infection. Those that

survived the acute infection were euthanized 11 days following surgery and examined for transcutaneous palpability of the abscesses. Upon opening, the odor of the peritoneal cavity was recorded, the presence of splenomegaly was recorded, and abscess formation at the liver, spleen, abdominal wall, retro hepatic gutter, colonic gutter, bowel, and omentum was graded by two separate observers in a blinded randomized manner based on a 5-point scale as: 0=no abscesses present at site, 0.5=one very small abscess present at site, 1=several small abscesses present at site, 2=medium to large abscesses present at site, and 3=one very large abscess present at site.

No significant differences in mortality were observed between the surgical control group, Ringer's Lactate control groups, INTERGEL™ Solution-treated groups, or the low dose volume Hyskon group. In contrast, administration of 15 mL/kg Hyskon significantly increased the mortality associated with the induced bacterial peritonitis. No significant differences in abscess scores for the liver, bowel, omentum, or "Other" sites were observed between any of the treatment groups. In contrast, treatment with INTERGEL™ Solution and Hyskon (both dose volumes) produced significant decreases in abscesses in the abdominal wall and in total abscess formation relative to the surgical control group. The low dose INTERGEL™ Solution group also had a significantly lower total abscess score than the low dose Ringer's Lactate control group.

The results of this study demonstrate that intraperitoneal administration of INTERGEL™ Solution at dose volumes up to 15 mL/kg does not potentiate mortality or abscess formation following bacterially-induced peritonitis.

**New text:**

*This study was repeated at the request of FDA, using a model of mixed bacterial flora with a larger group of animals, powered to detect a difference between LD<sub>50</sub> and LD<sub>75</sub> at the clinical dose of 5ml/kg. In this study, no difference on mortality or abscess formation was observed in animals treated with lactated Ringer's solution compared with INTERGEL® Solution.*

## **2. Absorption, Distribution, and Excretion Studies**

Several exploratory absorption, distribution, and excretion studies were

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conducted in rats, dogs and monkeys in which serum levels of HA and iron were determined following i.p. administration of FeHA.

The iron disposition in animals following i.p. administration of INTERGEL™ Solution was not found to be remarkably different from the normal variations observed in animals administered the saline control. Slight increases in serum iron were observed within the first 24 to 48 hours following dose administration, however, wide variations in individual animal data prevent any meaningful conclusions from being drawn.

Serum HA concentrations were shown to increase relative to FeHA and INTERGEL™ Solution administered intraperitoneally to rats, dogs and monkeys. Elevated serum HA levels are transient and do not suggest accumulation at the clinical intended dose (5 mL/kg), or even at doses up to 30 mL/kg. Serum HA concentrations consistently returned to near pre-dose HA levels within 7 days or earlier, depending on the dose; the greater the dose, the longer the time required to return to pre-dose levels.

Information from the autoradiography study in rats demonstrated that the pattern, mechanism, and extent of absorption, distribution, metabolism, and elimination of exogenous HA from the i.p. administered FeHA formulation appears to be the same as exogenous HA administered as HA alone. The tissues responsible for endogenous HA clearance also appear to efficiently metabolize the exogenous HA, returning serum levels of HA to pre-dose concentrations within days to a week of administration, depending on the dose. The only difference between the two formulations appears to be a slightly longer residence time at the site following i.p. administration of FeHA. This delay in absorption of FeHA, relative to HA, from the peritoneal cavity is most probably due to the greater viscosity of the ionically crosslinked formulation. Comparing the lymphatic absorption rates of HA and FeHA (0.38 and 0.19  $\mu\text{g}$  equivalents per gram of tissue per hour, respectively), the time to eliminate FeHA from the peritoneum is approximately twice that of HA.

Considering that the average flow rates of lymph through the thoracic duct in humans and rats are 125 mL/hr and 1.6 mL/hr, respectively, and that the intraperitoneal clearance of HA is the rate of total lymph turnover per unit body weight, then the weight-adjusted flow rates of a human (60 kg) and a rat (0.25 kg) would be 2.1 mL/kg/hr and 6.4 mL/kg/hr, respectively. Thus, the elimination half-life ( $T_{1/2}$ ) of HA from the peritoneum in humans would be expected to be 3.05 times the observed half-life ( $T_{1/2}$ ) of 8.4 hours in the rat (1), or approximately 25.62 hours. Added to this current

observation that the clearance rate of FeHA from the peritoneum is approximately half that of HA, then the elimination half-life ( $T_{1/2}$ ) of FeHA in humans is expected to be approximately 51 hours.

### **3. Effectiveness of FeHA in Other Animal Models**

- **Rat Cecum/Liver Model**

Preclinical evaluations were conducted in three studies with the rat cecal/liver adhesion model, developed to simulate "tough" adhesions that may be difficult to prevent. In each study, the cecum was exposed through a ventral midline incision, exteriorized and abrasions made by wiping the cecum with gauze until punctate bleeding developed. Three 8 mm lesions were created on each side of the abdominal wall by removing a layer of the peritoneum and transverse abdominal muscle with a stainless steel biopsy punch. All accessible surfaces of the liver were abraded by rubbing them with the wooden end of a sterile swab. The injured sites received one of various test materials including FeHA. Animals in the surgical control group did not receive any treatment. The sites were examined for the extent of adhesions 7 days later. In all cases, FeHA-treated groups had significantly ( $p \leq 0.05$ ) reduced adhesions to the cecum and the liver lobes compared with the control group.

- **Rabbit Thoracic Model**

The efficacy of FeHA in the rabbit thoracic model was evaluated in two studies. In each study, a 5 cm midline sternotomy was made. Fatty tissue covering the pericardium was removed using gauze, and a 2.5 cm incision pericardiotomy was performed. The exposed surface of the heart was abraded with gauze 10 times. No other abrasion was performed. The pericardium was left open. Animals received one of several treatments including FeHA; those in the surgical control group did not receive any treatment. The results from the FeHA-treated groups were suggestive of a beneficial effect of INTERGEL Solution at reducing adhesions.



#### **4. Packaging Qualification and Stability Testing**

To support broad commercial distribution of INTERGEL™ Solution, the packaging configuration was modified from that used during the initial clinical studies.

The original configuration used through the initial clinical evaluations consisted of aseptically packaging the gel in 100 mL Type 1 borosilicate amber vials with 20 mm flip tear-off seals. Three filled vials were labeled, cushioned in bubble-wrap, and packaged in a corrugated carton along with the instructions for use.

The alternative packaging configuration, which is more conducive to mass production and distribution, consists of subjecting the gel to a blow-fill-seal (BFS) operation where 320mL of gel material is filled into a bellow container (40% low density polyethylene / 60% high density polyethylene).

BFS is an automated process by which the bellow containers are formed, filled, and sealed in one continuous operation. The filled bellow container is placed in a thermoformed PETG (polyethylene terephthalate, glycol modified) tray along with a polyvinylchloride (PVC) trocar extension tube. The tray is sealed with a Tyvek lid to form a blister package. The sealed blister packages are sterilized via validated vaporized hydrogen peroxide (VHP plasma method) process.

Qualification and validation testing for the alternative packaging configuration consisted of the following: a) Biocompatibility Testing of the Bellow Material, b) Sterile Process and Filling Validation, c) VHP Sterilization Validation Testing, d) Tray Seal Validation Testing, e) Functionality Testing of the Delivery System, and f) Stability Studies.

##### **a. Biocompatibility Testing of the Bellow Material**

Class VI USP biocompatibility testing was performed on the INTERGEL™ Solution bellow material (40% low-density polyethylene / 60% high-density polyethylene) to determine the biological response of animals to direct and indirect contact with the bellow material or injection of the bellow material extract.

The bellow material did not produce a biological response following intramuscular implantation in rabbits, intracutaneous injection in rabbits, or systemic injection in mice. Therefore, the material used for

the bellow containers meets the requirements of USP XXIII, 1995, for Class VI Plastics-50°C.

**b. Sterile Processing and Filling Validation:**

INTERGEL™ Solution is filter sterilized with aseptic processing. Aseptic processing is a method where the product, container and closure are subjected to separate sterilization processes and then combined together while maintaining sterility. This method is recognized as an acceptable method of sterilization for those materials that cannot be terminally sterilized.

Validation of the sterile processing and filling of INTERGEL™ consisted of three phases of testing a) Process Media Fill Validation, b) Tote Media Fill Sterile Hold Validation and finally c) Blow-Fill-Seal Media Fill Validation. These three phases were intended to represent the three stages of the aseptic processing: filtration of product and the filling of a bulk tote container in preparation for transit to the packaging facility, the transfer of the bulk tote container to the packaging facility, and the filling of the bellows containers using a blow-fill-seal (BFS) process at the packaging facility.

**i) Process Media Fill Validation**

Testing was performed to validate and demonstrate that the first stage of the aseptic process; which involves the formulation, filtration and bulk filling of INTERGEL™ Solution into a bulk tote container; consistently produces sterile product.

Testing involved simulated formulation, filtration, and bulk filling of a 1000 liter tote container. Samples were diverted throughout the simulation, incubated, and visually inspected for sterility after 7 and 14 days. Growth promotion testing was performed on two of the samples at the zero and 14-day timepoint. All filters used during the process were pre and post use integrity tested to ensure they remained integral when used at the specified pressure and temperature.

All acceptance criteria were met. This testing validated the successful and consistent aseptic processing and filling of a bulk container.

## ii) Tote Media Fill Sterile Hold (Media Fill "B") Validation

Testing was performed to validate and demonstrate that the second stage of the aseptic process, which involves filling of the bulk tote container from the production formulation tank and transfer of this tank to the contract filler / packager, consistently produces sterile product.

Testing involved simulated formulation, filtration, filling, storage, and transfer of a 1000-liter tote. Throughout the filling of the tote, samples were diverted for further testing. The 1000-liter tote was stored at ambient temperature (15-25°C) for 40 days. After this 40 day hold time, the 1000 liter tote was shipped to the contract filler / packager in a truck with a temperature maintained at 2-30°C. This process was performed in triplicate.

The sample bags were incubated for 7 days at 20 - 25°C, then for another 7 days at 30-35°C, and finally incubated for a minimum of 26 days at 20-25°C. After each 7, 14, and 40 day incubation period was complete, four sample bags from each tote were examined for growth. Growth promotion testing was performed using one sample bag both on day zero and at the end of the 40 day hold time.

All acceptance criteria were met. It was demonstrated that the procedure for transferring sterile product into 1000-liter transfer totes, and storing the totes for a maximum of 40 days at 15-25°C, is capable of consistently producing and maintaining sterile product.

## iii) Blow-Fill-Seal Media Fill Validation

Testing was performed to validate and demonstrate that the third stage of the aseptic process, which involves the blow-fill-seal operation, consistently produces sterile product.

Testing involved simulating the blow-fill-seal (BFS) process. Test media was transferred from the bulk tote container to a 250-gallon storage tank via a peristaltic pump, and then moved by compressed air through transfer lines to the BFS. Test media was subsequently filled into 320-mL bellow containers. The media filled containers were inverted to wet all inner surfaces, and then incubated for 14 days at 20-25°C. At the end of the 14-day

incubation, the bellow containers were visually inspected for sterility. Several of these media filled bellow containers were then inoculated with challenge organisms for growth promotion testing to demonstrate the media could still support microbial growth.

All acceptance criteria were met. This testing validated the successful and consistent aseptic filling of INTERGEL™ Solution into 320 mL BFS bellow containers.

**c. VHP Sterilization Validation Testing:**

INTERGEL™ Solution is aseptically filled into bellow containers. These containers, along with PVC trocar extension tubing, are packaged in PETG thermoformed trays and sealed with Tyvek lids. The sealed blister packs are then terminally sterilized using vaporized hydrogen peroxide (VHP) to ensure that the outside of the bellow container and the trocar extension tube remain sterile.

The VHP sterilization process is performed by placing the sealed blister packages (containing bellow containers filled with INTERGEL™ Solution and the trocar extension tube) into sterilization tubs. The tubs are placed inside the chamber of the sterilizer. The chamber is closed and a vacuum is drawn. Vaporized hydrogen peroxide is generated and introduced into the chamber. The VHP fills the chamber and penetrates the porous TYVEK lid and fills the blister package. An ignition source in the chamber causes a plasma reaction, which converts the VHP to water vapor and oxygen gas. The combined effects of the VHP and the plasma reaction provide an effective sterilization of the bellows container and extension tube.

Testing was performed to demonstrate that the hydrogen peroxide sterilization process is effective in achieving a minimum Sterility Assurance Level of  $10^{-6}$  for packaged INTERGEL product. This validation study used a ½ cycle as the "worst case" for hydrogen peroxide gas plasma process parameters. Actual product will go through an "overkill" (one complete) cycle.

The STERRAD 100 chamber was loaded with 18 sealed INTERGEL™ Solution packs according to the specified load diagram. Twenty biological indicators (BI's) containing *Bacillus stearothermophilus* and six temperature sensors were placed throughout the load. The BI locations included areas most difficult to sterilize. Four sterilization

cycles were performed with the sterilizer parameter settings.

After processing, the biological indicators were incubated for 14 days at 55-60°C for sterility testing. Two unprocessed biological indicators previously set aside as positive controls were incubated to confirm viability. Data was analyzed from the temperature sensors, which monitored temperature throughout the cycle. Natural product bioburden was determined to ensure product bioburden was less than the biological indicator challenge.

All acceptance criteria were met. It was demonstrated that the hydrogen peroxide gas plasma sterilization process for INTERGEL™ Solution is capable of achieving a minimum Sterility Assurance Level of  $10^{-6}$  on the external surface of the bellow container.

#### **d. Tray Seal Validation Testing**

After aseptically filling the bellow containers with the INTERGEL™ Solution, the filled bellows are packaged in PETG thermoformed trays, along with PVC extension tubing, and sealed with Tyvek lids. The sealed blister packs are then sterilized using a hydrogen peroxide gas plasma cycle. Testing was performed following the sterilization cycle to validate the process used to seal Tyvek lids onto the thermoformed PETG trays as well as to demonstrate an acceptable seal strength.

The study was divided into three groups to reflect the lower (220°F), optimum (230°F) and upper limit (240°F) heated platen temperature limits for the tray sealer. The other critical operating parameters, which remained constant for all three groups included an 80 psig seal pressure and a 3.0 second dwell time. A total of 36 trays were sealed and tested, with 12 in each group. Each group had two runs of six trays each, with the tray sealer shut down between runs.

All acceptance criteria were met. It was demonstrated that the process used to seal Tyvek lids onto thermoformed trays containing INTERGEL™ Solution containers can consistently and with a high degree of assurance provide a seal with acceptable strength.

#### **e. Functionality Testing of the Delivery System**

INTERGEL™ Solution is intended to be dispensed directly into the patient during a laparotomy surgery or with the aid of a 5 ¾" length

extension tube. During a laparoscopy surgical procedure the product can be dispensed with the extension tube and a 5 mm surgical trocar. Testing was performed to evaluate and verify the delivery system design when used in either situation.

Bellow containers were tested during three evaluations and were divided into test groups according to viscosity, type of surgery simulated, and type of trocar. Samples were randomly divided between four technicians who were instructed to dispense as much of the contents as possible from each bellow. Bellow containers were weighed before and after dispensing to determine delivery volume. Functional performance was assessed using deliverable volume, dispensing time, bellow condition after dispensing, absence of spurs on the bellow ribs, ability of extension tube to stay on the bellow spout during expression, and the extension tube fit on the trocar.

All acceptance criteria were met following implementation of a consistent delivery technique. The INTERGEL™ Solution delivery system design is functional for use in both laparotomy and laparoscopic surgical procedures. The IFU was revised to describe the proper technique of instillation of INTERGEL Solution from a bellow container.

#### **f. Performance Testing of Product Shipping Cartons**

INTERGEL™ Solution packaging was subjected to design qualification testing to demonstrate that the package configuration was able to withstand the shipping environment.

The performance testing involved exposing the INTERGEL™ Solution packaging to simulated handling, vehicle stacking, and vibration (loose load and vehicle) tests. After subjecting the shipper boxes to simulated shipping and handling conditions, the following tests were performed: 1) bubble immersion leak testing of blister packages, 2) peel back testing, 3) visual inspection of blister packages for damage and 4) visual inspection of bellow containers for damage.

All acceptance criteria were met. The INTERGEL™ Solution package configuration was found to withstand the conditions of shipping.

### g. Stability Studies

Stability studies were completed to support the shelf life of the product using the bellow packaging configuration.

Samples of bellow containers or vials are randomly selected from each manufacturing batch for stability and shelf life testing. Units are randomly assigned to refrigerated storage at  $5\pm 3^{\circ}\text{C}$ , room temperature storage at  $25\pm 2^{\circ}\text{C}$  or  $30\pm 2^{\circ}\text{C}$ , and to accelerated storage conditions at  $40\pm 2^{\circ}\text{C}$ . Bellow container units are randomly pulled from storage for testing at 1, 2, 3, 6, 9, 12, 18, 24, 30, and 36 months (except for accelerated testing). Each unit is tested according to some or all of the following product specifications according to the test schedule: viscosity, pH, osmolality, hyaluronic acid assay, iron assay, endotoxin, cytotoxicity (bellow container only), package integrity, and appearance.

Accelerated shelf life calculations are performed using the viscosity values of units stored at  $40\pm 2^{\circ}\text{C}$  at 1, 2, 3, 6, and 9 months.

All testing to date has met the current acceptance criteria. Based on the accelerated bellow data, INTERGEL™ Solution, packaged in the bellow container, has been found to have a shelf-life of 24 months when stored at  $15 - 30^{\circ}$  or  $2-8^{\circ}\text{C}$ .

### J. SUMMARY OF CLINICAL EVALUATIONS:

INTERGEL Solution has been studied in controlled multicenter clinical investigations in female patients undergoing peritoneal cavity surgery by laparotomy with a planned second-look laparoscopy. Patients were administered 300 mL of INTERGEL Solution or lactated Ringer's Solution as an intraperitoneal instillate at the completion of the laparotomy procedure. INTERGEL Solution was shown to significantly reduce the incidence, extent and severity of adhesions throughout the abdominal cavity when used as an adjunct to good surgical technique. *New text: These results were obtained by evaluating surgical adhesions at 24 sites (including the adnexa) utilizing the standard methodology originally developed by the American Fertility Society for adnexal adhesions. When utilized to score adhesions at sites other than the adnexa, this adhesion scoring methodology is referred to as the Modified AFS score.*

A randomized, third-party blinded, parallel group, placebo-controlled, multicenter clinical study of safety and effectiveness of INTERGEL Solution was

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conducted. Female patients aged 18.6 to 45.9 years undergoing peritoneal cavity surgery by laparotomy received a single intraperitoneal instillation of 300 mL of INTERGEL Solution or lactated Ringer's solution to reduce post-surgical adhesion formation. Efficacy was evaluated approximately 6 to 12 weeks after the initial surgery during a second-look laparoscopic procedure. Two hundred eighty-one patients were evaluable for safety and 265 were evaluable for efficacy.

The primary efficacy variable was the Modified AFS score based on 24 anatomical sites in the pelvis and abdomen. Secondary efficacy variables were the proportion of sites with adhesions and the extent and severity of adhesions. Adhesions were characterized as *de novo* versus reformed, surgical versus non-surgical, and pelvic versus abdominal. Adhesions at all surgical sites, pelvic sites only, general surgical sites only, and at each individual anatomical site were evaluated. Safety was assessed based on adverse events recorded throughout the study, on clinical laboratory tests performed at baseline and post-therapy, and on gross evaluation at second-look.

Treatment with INTERGEL Solution in patients undergoing peritoneal cavity surgery was found to be superior to treatment with lactated Ringer's solution in reducing post-surgical adhesions. When all adhesion sites were considered, INTERGEL Solution was found to be significantly more effective than lactated Ringer's solution in reducing post-surgical adhesions based on an adhesion scoring method of the American Fertility Society (AFS), applied to 24 anatomical sites (modified AFS score). Patients treated with INTERGEL Solution had an overall average score that was 45% lower than that of patients treated with lactated Ringer's solution. The proportion of sites with new adhesions, and the severity and extent of post-surgical adhesions were also significantly reduced in patients treated with INTERGEL Solution. **Note: The following text appears in the original SSE and is unchanged.** *Treatment with INTERGEL Solution was also found to be significantly more effective than the control solution in reducing de novo and reformed adhesions, and adhesions at surgical and non-surgical sites.*

When the abdominal sites or pelvic sites were considered separately, INTERGEL Solution was found to be significantly more effective than the control solution in reducing the incidence, extent and severity of adhesions, *de novo* and reformed adhesions, and surgical and non-surgical adhesions. Similarly, a reduction in adhesions with INTERGEL Solution was observed in patients with endometriosis as well as those without endometriosis, whether sutures were used, and regardless of the method of adhesiolysis,



i.e. sharp dissection, blunt dissection, or cautery (lasers were used too infrequently to comment). A reduction in adhesions with INTERGEL Solution was also found for all subgroups of patients based on the surgical procedure performed: patients with excision of endometriosis, myomectomy, adhesiolysis, tubal procedures, ovarian procedures including removal of dermoids and endometriomas.

**Note: The following text appears in the original SSE and is unchanged:**

*The effect of INTERGEL Solution on reducing adnexal adhesions was shown by a significant reduction in the Standard AFS score compared to lactated Ringer's solution. The minimum score of both the right and left adnexa was reduced by 59% following administration of INTERGEL Solution. In addition, the proportion of patients with minimal scores (Standard AFS score 0-5) increased in the patient group that received INTERGEL Solution and decreased in the lactated Ringer's solution group.*

*Similarly, the proportion of patients with mild, moderate or severe Standard AFS scores (6-10, 11-20, 21-32, respectively) decreased in the group that received INTERGEL Solution and increased in the group that received lactated Ringer's solution.*

The safety profile of patients treated with INTERGEL Solution was comparable to those treated with lactated Ringer's solution. All patients in both treatment groups reported having at least one adverse event. The most frequently reported patient complaints in both treatment groups were pain, nausea, constipation, headache, abdominal pain, and flatulence. These expected events (given that patients were undergoing anesthesia and surgery) were generally mild to moderate and all resolved spontaneously or with treatment. Sixteen (11.2%) patients treated with INTERGEL Solution and five patients (4.7%) treated with lactated Ringer's solution experienced adverse events considered by the investigator to be possibly, probably, or definitely related to treatment. These events included abdominal and/or post-operative pain, fever, nausea, and constipation, and all resolved spontaneously or with treatment. Treatment-related serious adverse events were experienced by four patients in the INTERGEL Solution group (two cases of abdominal pain, one case of fever, and one case of post-operative ileus) and one patient in the lactated Ringer's solution group (fever). These patients were treated with medications or additional surgical procedure. There were no discontinuations due to an adverse event and no deaths occurred during the study.

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As expected in patients who had undergone recent surgery, normal to low or high shifts in several clinical laboratory parameters occurred in both treatment groups within 3 days of the initial surgery (Visit 1), reflecting factors such as surgical trauma and hemodilution. By Visit 3 (immediately prior to the second-look laparoscopy), most parameters were within the normal ranges in both treatment groups. Shifts outside the normal ranges were considered not clinically significant. Elevations in WBC's, primarily due to an increase in the number of neutrophils, first seen at Visit 1, persisted through Visit 2, and returned to normal by Visit 3. Subgroup analysis indicated that there was no correlation between elevated WBC concentrations and center, continent, fever, adhesion formation (Modified AFS score), duration of hospitalization, surgical time, and blood loss. No clinical sequelae (including infection and intraperitoneal adhesions) with patients with elevated WBC and/or neutrophils shifts was identified which was considered to be clinically significant. Since these findings of a low, transient elevation of WBC concentration was not common to any particular center, demographic, or clinical manifestation, it was considered to be a brief, subclinical response without clinical significance.

#### K. CONCLUSIONS:

A single intraperitoneal instillation of 300 mL of INTERGEL Solution in female patients undergoing peritoneal cavity surgery by laparotomy was safe and effective in improving adhesion outcome:

- The mean Modified AFS score for 24 sites throughout the peritoneal cavity was significantly ( $p < 0.05$ ) lower in the INTERGEL Solution group than in the lactated Ringer's solution group.
- The minimum Standard AFS score of both the right and left adnexa was significantly ( $p < 0.05$ ) lower in the INTERGEL Solution group than in the lactated Ringer's solution group.
- The proportion of sites with post-surgical adhesions were significantly ( $p < 0.05$ ) fewer in the INTERGEL Solution group than in the lactated Ringer's solution group.
- The severity and extent of post-surgical adhesions were significantly ( $p < 0.05$ ) less in the INTERGEL Solution group than in the lactated Ringer's solution group.
- *De novo* and reformed adhesions were significantly ( $p < 0.05$ ) reduced in the INTERGEL Solution group than in the lactated Ringer's solution group.
- The reduction in adhesions was observed whether all 24 sites were considered, only the general surgical sites were considered, or only the

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- pelvic sites were considered.
- The reduction in adhesions was observed regardless of the presence or absence of endometriosis, the use of sutures, the method of adhesiolysis, or the surgical procedure, including myomectomy, adhesiolysis, tubal and ovarian surgery.
  - The safety profile (i.e., adverse event incidence rates, clinical laboratory test results) of patients treated with INTERGEL Solution was comparable to those treated with lactated Ringer's solution.